In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 15-247V

(to be published)

* *	Special Master Corcoran
JASMYNE GRAMZA, *	
*	
*	
Petitioner, *	Filed: February 5, 2018
*	
v. *	
*	Entitlement; Althen Prong Three;
SECRETARY OF HEALTH *	Medically Acceptable Timeframe;
AND HUMAN SERVICES, *	Human Papillomavirus ("HPV");
*	Immune Thrombocytopenic Purpura
Respondent. *	("ITP").
*	
* *	

Andrew D. Downing, Van Cott & Talamante PLLC, Phoenix, AZ, for Petitioner.

Darryl R. Wishard, U.S. Dep't of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

On March 10, 2015, Mrs. Tarah Gramza filed a petition for compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program") on behalf of her then-minor[2] daughter, Ms. Jasmyne Gramza.[3] The Petition alleged that as a result of Human Papillomavirus ("HPV" or "Gardasil") vaccinations that she received on January 7, 2012, July 26,

[1] This Decision will be posted on the United States Court of Federal Claims website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet.** As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Decision will be available to the public in its current form. *Id.*

[2] The caption of the case was updated to identify Ms. Gramza as Petitioner after she reached the age of majority. Ex. 1.

[3] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended, 42 U.S.C. §§ 300aa-10 through 34 (2012) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act without inclusion of that statutory prefix.

2012, and January 23, 2013, Ms. Gramza experienced immune thrombocytopenic purpura ("ITP").[4] Petition at 1, 6.

An entitlement hearing was held in the matter on June 6-7, 2017, and after the filing of simultaneous post-hearing briefs, this case is now ripe for my consideration. For the reasons stated in more detail below, I find that Petitioner has not carried her burden of proof in establishing that onset of her ITP occurred in a medically acceptable timeframe, or that the vaccine more likely than not caused her ITP.

I. Factual History

Vaccination

Petitioner was born on December 6, 1999. Ex. 3. at 1. Her medical records indicate that she had a history of migraines and contracted pneumonia in 2012, but had no other notable or relevant health problems before receiving the first HPV vaccine dose. *Id*. at 32, 35, 39.

On January 7, 2012, Ms. Gramza received her first dose of the HPV vaccine at 13 years of age. Ex. 3 at 10. The record does not reveal any reaction to that vaccination of any kind relevant to the claim in this case. She received her second dose on July 26, 2012, when she was also treated by Dr. H. Glenn Garner at East Valley Pediatrics ("EVP") in Mesa, Arizona, for an unresolved large hematoma[5] on her left thigh, incurred after falling off a pool deck two months prior. *Id*. at 25. Petitioner reported that the bruise had faded, but the area of injury remained swollen and was tender to the touch (and at hearing a photo of the injury was offered to corroborate its existence). *Id*.; Ex. 89; Tr. at 10-11, 58-59. Dr. Garner directed Petitioner to use a heating pad and to follow-up in four months. *Id*. at 26.

There is another months-long gap in the medical records, with no evidence of any problems arguably related to the vaccine. Then, Ms. Gramza returned to Dr. Garner for another well-child visit at EVP on January 23, 2013. At this time she received her third dose of the Gardasil vaccine. No concerns were noted about bruising or any other intervening symptoms experienced in the approximately six months since Petitioner had last seen Dr. Garner. *Id*. at 18-20.

Documented Evidence of ITP

[4] ITP was previously often referred to as "idiopathic" thrombocytopenic purpura, but today the preferred term for the disease is "immune" thrombocytopenic purpura, because the condition is understood to involve an autoimmune process involving antibody attacks against platelets. *Johnson v. Sec'y of Health & Human Servs.*, No. 14-113V, 2017 WL 772534, at *5 (Fed. Cl. Spec. Mstr. Jan. 6, 2017).

[5] A hematoma is a localized collection of blood, usually due to a break in the wall of a blood vessel. *Dorland's Illustrated Medical Dictionary* 832 (32nd ed. 2012) (hereinafter "*Dorland's*").

Over a year after her last dose of the HPV vaccine, Petitioner returned to EVP on February 11, 2014, reporting that "over the last 6 months or so, pt. has bruised more easily and some seem a lot larger than they should be for the injury." Ex. 3 at 15. Dr. Trupti Amin-Chapman, who was one of Petitioner's primary care physicians, ordered lab testing which showed that Petitioner had a low platelet count (23,000 platelets per microliter of blood) and a high prothrombin time "(PTT")[6] of 50.9. *Id*. at 63, 75-76. Two days later, on February 13, 2014, Petitioner saw Dr. Christine Knoll, a hematologist at Phoenix Children's Hospital ("PCH"), in Phoenix, Arizona, at Dr. Amin-Chapman's direction. Ex. 4 at 86. Dr. Knoll recorded that Ms. Gramza claimed to have begun noticing her symptoms around July 2013 (about six months after her final dose of HPV vaccine in January 2013), when she would experience large bruising, either spontaneously or after a small injury. *Id*. Petitioner's evaluation was otherwise normal, however, including a family history that was absent any blood disorders. *Id*. at 87. Dr. Knoll reviewed the EVP lab work and performed additional testing, which produced normal results except for Epstein Barr Virus ("EBV") titers[7] suggestive of past infection. *Id*. at 88. Dr. Knoll instructed Petitioner and her parents that Petitioner's condition was possibly autoimmune – most likely lupus. *Id*.

On February 16, 2014, Petitioner noticed petechiae,[8] and she visited the emergency room at PCH. Ex. 4 at 81-82. A few days later, on February 21, 2014, Petitioner saw Dr. Kaleo Ede, a rheumatologist, at which time her parents related a history similar to what they had said the week before, i.e., gradual onset of worsening fatigue over the past six months, and headaches for several years (although, as noted above, such symptoms were *not* reported after either of the first two HPV doses). Although Petitioner's exam was normal, Dr. Ede recommended further evaluation for lupus. Ex. 3 at 59-61.

Shortly thereafter a hematologist, Dr. Sanjay Shah, reviewed Petitioner's lab results, which indicated that she had a prolonged PTT. Ex. 4 at 71. Ms. Gramza also had a positive antibody screen, normal iron studies, and a negative Coombs test[9] result, which Dr. Shah interpreted as evidencing the presence of a lupus anticoagulant. *Id*. Nevertheless, despite such "red flags" in her case, Dr. Shah diagnosed Ms. Gramza with autoimmunity and chronic ITP rather than lupus, recommending observation and additional lab studies. *Id*.

---

[6] Prothrombin time ("PTT") is one measurement of the body's ability to use clotting factors to stop bleeds. *Dorland's* at 674.

[7] Epstein Barr Virus causes infectious mononucleosis, more commonly referred to as mono, an acute disease characterized by fever, pharyngitis, atypical lymphocytes, and lymph node and splenic enlargement. *Dorland's* at 1177. An EBV titer can measure whether an individual has previously experienced an EBV infection. *Id.* at 2061.

[8] Petechiae are small pinpoint skin rashes due to insufficient platelets. *Dorland's* at 1422.

[9] A Coombs test, also known as an anti-globulin test, looks for the presence of nonagglutinating antibodies against red blood cells. *Dorland's* at 1885.

Ms. Gramza returned to Dr. Shah on March 28, 2014, for analysis and treatment of her ITP. She now complained of some bruises with fatigue, intermittent diffuse joint pains, and sore muscles. Ex. 4 at 56. Dr. Shah opined that Petitioner's ITP was most likely autoimmune in origin, but because her platelet count had risen to 34,000, she was not at risk for significant bleeding. *Id*. at 58-59. Dr. Shah also discussed possible treatments for chronic ITP, and he recommended holding off on deciding on a further course of treatment.

On April 30, 2014, Ms. Gramza again saw Dr. Ede for evaluation of her abnormal antibody levels. Ex. 4 at 50. Petitioner continued to display low platelet counts, and reported nosebleeds twice a week, bleeding gums after brushing her teeth, spontaneous bruising, and heavy menses. *Id.* She also had some fatigue and occasional joint pain, but no joint swelling, skin rashes or other problems. *Id*. at 51-52. Dr. Ede expressed the view (previously endorsed by Dr. Shah) that Petitioner did not meet the criteria for lupus, but she unquestionably had ITP in need of treatment. Ex. 3 at 48-50.

The following month, on May 14, 2014, Petitioner sought urgent care at PCH for several nose bleeds and two weeks of prolonged menses. Ex. 4 at 46. Testing revealed her platelet count was low again at 13,000, and her hemoglobin count was 10.6. *Id.* at 46-47. Ms. Gramza was discharged for a hematology evaluation the next day. *Id*. At that time she saw Dr. James Williams, and she complained of fatigue and joint pains. Her low platelet count was confirmed. *Id*. at 42.

Ms. Gramza was now treated with IVIG.[10] This treatment proved initially effective, and by May 21, 2014, testing revealed a platelet count increase to 135,000. Ex. 4 at 46-47. But when she returned to Dr. Williams on June 17, 2014, her count was down to 4,000, suggesting that IVIG had produced only a temporary "bump" in platelets. *Id*. at 23. The treatment plan indicated that Ms. Gramza was tolerating Rituximab[11] well and received her third of four doses at the visit, along with steroids for four days. *Id*. She also received her first dose of Depo-provera[12] for heavy menses that had begun two weeks prior. *Id.* at 23-24.

Over the next several months, Ms. Gramza's platelet counts improved after completing her last dose of Rituximab. Ex. 4 at 22. Later in June, Petitioner's platelet counts increased to 76,000,

[10] Intravenous immunoglobulin ("IVIG") is a blood product used to treat patients with antibody deficiencies, including neurological disorders. *Clinical Uses of Intravenous Immunoglobulin*, NCBI (2005), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1809480/ (lasted visited on Aug. 28, 2017). It is commonly prescribed to treat diseases believed to be autoimmune in nature, increasing the effectiveness of an individual's immune response.

[11] Rituximab – a monoclonal antibody that binds to CD20 antigens and is administered intravenously – is used in the treatment of autoimmune diseases like ITP. *Dorland's* at 1650. Ms. Gramza began this treatment on May 29, 2014 and tolerated it well. Ex. 4 at 23.

[12] Depo-Provera is the brand name of a long-acting contraceptive that is administered intramuscularly. *Dorland's* at 1120.

and then returned to normal levels of 225,000 in July 2014, decreasing to a still-normal level of 176,000 by August. *Id*. at 9, 13, 16, 22. As of October 2014, Petitioner was noted to have maintained normal platelet levels since July 2014 without the need for further treatment. *Id.* at 4-7. In December 2014, her platelet counts remained normal (at 258,000), although the migraine headaches of which she had complained for many years persisted. *Id.* at 1-3. By February 2015, the counts had declined but remained normal. Pet. Ex. 6. There is no subsequent medical record history relevant to the claim, as it does not appear that Ms. Gramza has suffered any platelet drops or ITP sequelae since the late summer of 2014.

II. Fact Witness Testimony

A. *Mrs. Gramza*

Mrs. Tarah Gramza, Petitioner's mother, was the first witness presented at the hearing. Transcript ("Tr.") 9-55. Mrs. Gramza described the Petitioner as a normal teen who did not participate in sports but had played the violin since she was in fourth grade. *Id*. at 10. She recalled being concerned about a potential vaccine reaction after Petitioner received her first Gardasil vaccine on January 17, 2012. *Id*. This concern stemmed from an accident a few months after vaccination (May 2012) when Petitioner fell on the pool deck, creating a large hematoma and a scratch on her thigh, which took many months to heal. *Id.* at 10-11. After Petitioner received the second dose of the vaccine on July 26, 2012, Mrs. Gramza remembered still being concerned about the hematoma, but Petitioner had no other symptoms. *Id*. at 11. (As noted above, the medical records reveal the hematoma was discussed during Petitioner's July 2012 doctor's visit, although no connection to the HPV vaccine was made).

Mrs. Gramza did not notice any other concerning symptoms that fall, but did recall something happening after Petitioner received the third dose of Gardasil on January 23, 2013. Tr. at 12. Around March 2013, Mrs. Gramza remembered seeing small bruises on Petitioner, but did not think doctor intervention was necessary because she thought they were from general contact areas or could be attributed to lack of iron in her diet. *Id*. By June 2013, however, Petitioner reported to Mrs. Gramza that she was continuing to bruise and did not know the origin of the bruises, but that they were not painful. *Id*. Mrs. Gramza began Petitioner on a vitamin regime, which included iron. *Id*. at 13.

In July 2013, the Gramzas went on a trip to Hawaii, which Mrs. Gramza remembered well. She recalled that Petitioner had recently started her period and on the flight to Hawaii, she had to change her clothes because of heavy menstrual bleeding that embarrassed her. Tr. at 13. On that trip, Petitioner was also pushed off a soft-sided boat, which Mrs. Gramza testified created a very large bruise on the back of Petitioner's leg, but again was not accompanied by any pain. *Id*. at 14. Up to this point, and through the summer of 2013, Mrs. Gramza (a former nurse) did not believe that the bruising was concerning enough to merit a doctor's appointment. However, by February

2014, Mrs. Gramza became worried after two more large hematomas appeared on Petitioner after a fight with her sister.

In response, Mrs. Gramza took Petitioner to Dr. Chapman in February 2014 for a general check-up, at which time she mentioned the concerns she was having about the persistent bruising. Tr. at 16. Dr. Chapman ran various blood and urine tests on Petitioner, revealing the alarmingly low platelet counts. *Id*. at 17. After those results, the Gramza family began to see hematologists to discover the source of the abnormality. *Id*. at 17-20. Mrs. Gramza recalled Dr. Ede opining that it could be lupus, but because Petitioner did not have kidney involvement or joint pain, that diagnosis was less likely. *Id*. at 19.

During the spring of 2014, Mrs. Gramza recalled Petitioner experiencing more severe symptoms, including skin that was yellow and appeared to be molting, along with increased petechiae. Tr. at 19. In addition, Petitioner had begun to have nose bleeds, more heavy menstruation, and fatigue. *Id*. at 19-20. After several treatments including IVIG and Rituximab, however, Petitioner's platelet count rose. *Id*. at 21-23. Mrs. Gramza did research, helped by her medical background, and discovered the articles of Dr. Yehuda Shoenfeld. *Id*. at 22-23. She thought that those articles provided support for vaccine causation of Petitioner's condition and shared them with Petitioner's treating physicians.

B. *Jasmyne Gramza*

The Petitioner also testified at the hearing. Tr. at 56-76. She recalled being healthy prior to her vaccinations and did not notice any symptoms immediately after (a few weeks) her first Gardasil vaccine in January 2012. *Id*. at 58. However, after she slipped and hit her leg at the pool in May 2012, she noticed that the bruise did not heal properly. *Id*. at 58-59. After receiving her second dose of Gardasil (in July 2012), Petitioner did not notice any similarly unusual bruising. *Id*. at 59. But following her third Gardasil vaccination in January 2013, Petitioner remembered bruising easily starting around March 2013. *Id*. at 60. Around the end of 2013, Petitioner also recalled having nosebleeds and bleeding gums. *Id*. at 65.

Petitioner confirmed that she did not see a doctor for her alleged ITP-related symptoms in 2013, mainly because she and her family downplayed the symptoms as a regular childhood occurrence. Tr. at 62. And, as observed in the recitation of the medical history, no such symptoms are contained in the 2013 records filed in this case. But she maintained her recollection of experiencing symptoms in 2013 was accurate, because at the time her family was in the process of moving to a new house in June 2013. *Id*. One month later, Petitioner went on the family trip to Hawaii recounted by her mother, and she remembered having a very heavy period on the plane, such that she bled through her outfit (which was very unusual for her, with most of her prior periods being very light). *Id*. at 63. She attributed this to be her "new normal." *Id*. Petitioner also reiterated what Mrs. Gramza said about her being pushed off the soft-sided boat while in Hawaii and

experiencing another unusual hematoma, adding that it did not hurt and that she was quite shocked at the size of the bruise that her mom noticed the night of the incident. *Id*. at 4.

Petitioner recalled an additional incident from December 2013 that she had not reported to her parents. Tr. at 65. Specifically, around her birthday in December, her parents had remodeled her room, including a new desk, and while Petitioner was working at the desk her nose suddenly began bleeding "like a faucet." *Id*. Petitioner did not seek help from her parents or a physician because she thought that "everybody gets bloody noses." *Id*. About two months later, however, Petitioner felt the need to see a doctor after she developed two large bruises (without accompanying pain) that "looked like somebody had probably like hit me with a baseball bat or like I had gotten in a car accident or something" after playing with her sister and bumping into a nightstand. *Id*. at 66. That visit was in February 2014 to her primary care physician, Dr. Chapman, at which time the low platelet count was first recorded. *Id*. at 68. At this visit, Petitioner did not tell Dr. Chapman about her heavy periods because she thought that was what all women experience and therefore not worthy of mention. *Id*. at 71. Petitioner similarly did not report the nose bleeds and gum bleeding she had been experiencing. *Id*. Finally, Petitioner confirmed that she has been in remission from ITP since June 2014. *Id*. at 68.

C. *Dr. Kaleo Ede*

Dr. Ede, one of Petitioner's treating physicians at PCH in Phoenix, Arizona, testified telephonically via video conference. Tr. at 115-27. He is currently a pediatric rheumatologist. *Id*. at 116.

Dr. Ede first saw Petitioner on February 21, 2014, and at that time noted clinical symptoms of "six months of gradually worsening fatigue as well as headaches for several years and not sleeping well at night. Additionally, she had been noticing mild bleeding of gums when she was brushing her teeth and also complaining of easy bruising." Tr. at 117. Because Petitioner was not exhibiting joint symptoms or problems with her kidneys, Dr. Ede determined that it was unlikely she suffered from lupus. *Id*. at 118-19. This determination was confirmed for Dr. Ede after he saw Petitioner in April 2014, when he determined that she did not meet the criteria for lupus that has been adopted by the American College of Rheumatology—ACR 1997 Classification Criteria ("ACR 1997"). At best, she displayed only three of the clinical elements—"positive ANA, hematologic criteria with thrombocytopenia, and immunologic criteria including positive double-stranded DNA and positive antiphospholipid antibodies." *Id*. at 120.

Dr. Ede recognized that although his notes contained an ITP diagnosis for Petitioner, it was beyond the scope of his practice, as a rheumatologist, to opine if that diagnosis were accurate. Tr. at 122. But he more confidently opined that Petitioner did not have lupus, based on her clinical history, exam findings, lab data, and her not meeting the ACR 1997 criteria. *Id*. He continues to follow her progress but has not seen her for a visit since June 2014.

At hearing, Dr. Ede was asked whether Ms. Gramza could be deemed to have suffered from lupus based on more recently-developed criteria (the Systemic Lupus International Collaborating Clinics ("SLICC")), given that she appeared to meet four of the five criteria,[13] but he stood by his initial assertion that Petitioner's clinical picture was inconsistent with a diagnosis of lupus. Tr. at 124. Dr. Ede emphasized that both sets of criteria are meant to determine only if a patient is an appropriate candidate for a clinical trial, rather than to be applied diagnostically. *Id*. at 135.

III. Expert Testimony

A. *Petitioner's Expert – Dr. Yehuda Shoenfeld*

Dr. Shoenfeld filed two expert reports and also testified at hearing. *See* Expert Report, dated Aug. 27, 2015, filed as Ex. 8 (ECF No. 20) ("First Shoenfeld Rep."); Expert Report, dated Feb. 1, 2016, filed as Ex. 66 (ECF No. 32) ("Second Shoenfeld Rep."); Tr. 79-113, 127-71. Dr. Shoenfeld opined that there was a causal link between Petitioner's series of vaccinations and her ITP. *See generally* First Shoenfeld Rep.

Dr. Shoenfeld identifies himself as the current head of the Center for Autoimmune Diseases, which he founded at the Sheba Medical Center in Israel. Shoenfeld CV, dated Aug. 17, 2015, filed as Ex. 9 (ECF No. 16). He is also the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at Tel Aviv University. *Id.* His experience focuses on autoimmune and rheumatic diseases, and he has published many peer-reviewed papers in journals and books on these topics. *Id.* He is on the editorial board of 32 journals in the field of autoimmunity. *Id.*

As a preliminary matter, Dr. Shoenfeld agreed that Ms. Gramza's proper diagnosis is ITP, opining that she did not have lupus (although he acknowledged that lupus can present with ITP). Tr. at 135-37. As Dr. Shoenfeld reasoned, Ms. Gramza's medical records did not reveal significant joint pain or limitation of motion, which in his view would characterize lupus. *Id*. at 136. Moreover (and other than the criteria she met for ITP), Petitioner did not have any other involvement in her systems (including her kidneys), which in his experience would be unusual in lupus, an "affliction of almost any organ or tissue in our body." *Id*. at 135-36. Petitioner's remission from ITP after treatment with Rituximab was further evidence to Dr. Shoenfeld that she did not have lupus, as he would not expect remission from lupus to persist for such a long period of time. *Id*. at 137-39.

In so testifying, Dr. Shoenfeld acknowledged that his opinion about Petitioner's diagnosis had changed over the course of his work on the case. His initial report had accepted lupus as the proper diagnosis, but he shifted to the position in his supplemental report that ITP was the better explanation. Tr. at 144. He attributed this change to the fact that in the process of his looking at

[13] Those four criteria are thrombocytopenia, presence of ANA, anti-DNA, and antiphospholipid antibodies. Tr. at 124.

the blood testing work for Ms. Gramza in the medical records, he concluded that the lack of disease progression without further organ involvement weighed against a lupus diagnosis. *Id*.

Dr. Shoenfeld specifically proposed that Ms. Gramza's ITP occurred via the biologic mechanism of molecular mimicry. First Shoenfeld Rep. at 12. As Dr. Shoenfeld testified, protein sequence homology exists between components of the HPV-16 virus contained in the vaccine (KATPTTS sequence) and blood platelets. *Id*., *citing* Darja Kanduc, *Quantifying the Possible Cross-Reactivity Risk of an HPV16 Vaccine*, 8 J. Experimental Therapeutics Oncology 65, 68 (2009), filed as Ex. 39 (ECF No. 23-10) ("Kanduc One"). As a result of this homology, "an autoantibody with subsequent generation of polyclonal autoantibodies" produced in response to the vaccine reacts with both the vaccine antigens and self-antigens on the platelet surface, causing the autoimmune process that destroys the platelet and results in ITP. First Shoenfeld Rep. at 13, *quoting* J. Despotovic, et al., *RhIG for the Treatment of Immune Thrombocytopenia: Consensus and Controversy (CME)*, 52 Transfusion 1126, 1129 (2012), filed as Ex. 60 (ECF No. 26-1).

In order to encourage this autoimmune reaction, Dr. Shoenfeld asserted, the adjuvant in the HPV vaccine would likely play a role. First Shoenfeld Rep. at 15. He described adjuvants as inflammatory substances that cause hyperactivity in the immune system. Second Shoenfeld Rep. at 3. Dr. Shoenfeld's second report expressly states that in the absence of an adjuvant, the immune system would limit any potential cross-reactions. *Id*. at 4. At hearing, however, he minimized his reliance on the adjuvant contributing to Petitioner's reaction, stating that the importance of the adjuvant is only about twenty percent of his causation theory. Tr. at 168.

Dr. Shoenfeld also referenced several pieces of medical literature that have reported an association between vaccination and ITP, although many of the cited items were not notably persuasive on close examination. Tr. at 87-88; M. Rinaldi, et al., *Anti-Saccharomyces Cerevisiae Autoantibodies in Autoimmune Diseases: from Bread Baking to Autoimmunity*, 45 Clinical Review Allergy Immunology, 152 (2013), filed as Ex. 15 (ECF No. 21-6) ("Rinaldi"); G. Pugnet, et al., *Immune Thrombocytopenic Purpura Following Human Papillomavirus Vaccination*, 27 Vaccine 3690 (2009), filed as Ex. 18 (ECF No. 21-9) ("Pugnet"). Rinaldi, for example, compiled data of instances of ITP following vaccination, but in no cases was the HPV vaccine so associated. Rinaldi at 11-12. Pugnet is a one-page letter to the editor describing the "first case of an acute immune thrombocytopenia purpura (ITP) following HPV vaccination." Pugnet at 1.

Dr. Shoenfeld himself co-authored a case report referenced by Petitioner detailing Ms. Gramza's alleged vaccine reaction. Mojca Bizjak, et al., *Vaccination and Secondary Immune Thrombocytopenia Antiphospholipid Antibodies by Human Papillomavirus Vaccine*, 53 Seminars in Hematology S48 (2016), filed as Ex. 90 (ECF No. 43-1) ("Bizjak"). Ignoring the self-referential character of this evidence, Bizjak also cites to a large empirical study that found no instances of increased new-onset autoimmune diseases out of a group of nearly 200,000 women who received the HPV vaccine, and no cases of ITP in particular. C. Chao, et al., *Surveillance of Autoimmune*

Conditions Following Routine Use of Quadrivalent Human Papillomavirus Vaccine, 271 J. Internal Medicine, 193 (2012), filed as Ex. J (ECF No. 28-6)("Chao"). Although Dr. Shoenfeld argued that the significance of the study was somewhat undercut by its authors' conflicts of interest,[14] Chao presents epidemiological evidence that is contrary to the causation theory alleged by Petitioner.[15]

Taking into account the lengthy amount of time it takes for sufficient platelets in the blood to be destroyed by an autoimmune process resulting in ITP, Dr. Shoenfeld opined the timing in this case was appropriate for vaccine causation, even if onset began around July 2013 (or about six months after vaccination). Tr. at 139-41. He did, however, acknowledge that although Ms. Gramza alleges she began experiencing symptoms around that time, blood testing was not performed until the following year, making it difficult to identify if in fact her platelet count had begun decreasing within six months of vaccination or occurred thereafter. *Id*. at 141.

Dr. Shoenfeld also asserted that Petitioner likely experienced a challenge/re-challenge[16] reaction in the course of receiving the three HPV doses that further corroborated the association between vaccination and injury herein. Tr. at 158. While there were no clinical manifestations following the first dose of the HPV vaccine, Petitioner's system was "re-challenged" by the second dose in July 2012, likely in the form of a drop in platelet count (although this cannot be confirmed given that no blood work was performed during this time). Then, after receiving the last dose of the HPV vaccine in January 2013, Petitioner experienced re-challenge yet again, with her most severe symptoms in the form of pronounced bruising with no explanation as well as a low platelet count that was found after blood testing (albeit not conducted until February 2014, or nearly seven months after the last dose). *Id*. at 159-60.

[14] The Chao article acknowledges that its lead authors received funding for the study from Merck & Co. The authors were also paid by Merck & Co., Pfizer, and Amgen for other unrelated studies. Chao at 10. The conflict of interest statement also asserts that the sponsor (Merck & Co.) "had significant input into the study design and analytic plan, all pre-specified in a protocol that was approved by the FDA, and took part in the review of analyses and drafting and revising the manuscript." *Id*.

[15] I have previously found Chao to be persuasive in cases involving injuries alleged to have occurred after receipt of the HPV vaccine. *See, e.g.*, *Johnson v. Sec'y of Health & Human Servs.,* No. 14-113V, 2017 WL 772534, at *19 (Fed. Cl. Spec. Mstr. Jan. 6, 2017) (HPV vaccine and ITP); *Sullivan v. Sec'y of Health & Human Servs.,* No. 10-398V, 2015 WL 1404957, at *19 (Fed. Cl. Spec. Mstr. Feb. 13, 2015) (HPV vaccine alleged to cause rheumatoid arthritis).

[16] Challenge/re-challenge is "a paradigm for exploring whether one substance caused an adverse reaction. Under this model, an individual who has had an adverse reaction to the initial vaccine dose (the challenge event) suffers a worsening of symptoms after a second or third injection (the re-challenge event.)" *Viscontini v. Sec'y of Health & Human Servs.*, No. 98-619V, 2011 WL 5842577, at *22 (Fed. Cl. Spec. Mstr. Oct. 21, 2011) (quoting *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 603 (2010) (quotations omitted)), *mot. for review den'd,* 103 Fed. Cl. 600 (2012)).

B. *Respondent's Experts*

1. Dr. Carlos Rose

Dr. Carlos Rose, a pediatric rheumatologist, filed two expert reports and testified at the hearing on Respondent's behalf. *See* Rose Expert Report, dated Nov. 23, 2015, filed as Ex. E (ECF No. 28) ("First Rose Rep."); Rose Supplemental Expert Report, dated Mar. 23, 2016, filed as Ex. FF (ECF No. 36-1) ("Second Rose Rep."); Tr. at 176-271. Dr. Rose opined that Petitioner has Systemic Lupus Erythematosus ("SLE"), and that her condition is not related to Petitioner's receipt of the HPV vaccines. First Rose Rep. at 8.

Dr. Rose is currently employed as the Division Chief for Rheumatology at Alfred I. du Pont Hospital for Children, and has worked as a physician for nearly 30 years. Rose CV, dated Nov. 23, 2015, filed as Ex. F (ECF No. 28), Tr. at 4. Dr. Rose attended the University of Buenos Aires before performing a residency in adult rheumatology in Argentina. Rose CV at 1; Tr. at 5. Thereafter, Dr. Rose moved to the United States and completed an additional rheumatology residency at Children's Hospital, in Philadelphia, Pennsylvania. Rose CV at 5; Tr. at 5. He was then hired for his current position. Dr. Rose is board certified in Pediatric and Adult Rheumatology, and Pediatrics. Rose CV at 5; Tr. at 5.

In his expert report, Dr. Rose began by asserting that Ms. Gramza's 2014 presentation could be deemed to satisfy four of the five SLICC criteria, making the SLE diagnosis appropriate. First Rose Rep. at 4; Tr. at 191-92. In particular, Petitioner displayed: (1) a thrombocytopenia platelet count of less than 100,000; (2) ANA antibodies; (3) Anti-dsDNA antibodies; and (4) Anti-phospholipid antibodies. First Rose Rep. at 4, Tr. at 191-92. This rendered ITP an inappropriate diagnosis, because "ITP is a condition with just thrombocytopenia, and she has more things that—than thrombocytopenia." Tr. at 200. Dr. Rose's second expert report, however, stated this conclusion less confidently, proposing only that "Jasmyne has *enough* features (albeit laboratory only) of pSLE and hence she requires a close follow up for the next few years." Second Rose Rep. at 1 (emphasis added). In any case, Dr. Rose rejected Dr. Shoenfeld's conclusion that Petitioner suffered from isolated ITP, given its connection to a lupus diagnosis. Second Rose Rep. at 2; Tr. at 200-01. He classified Petitioner's condition as mild lupus, relying on the lupus anticoagulant test result, and noting the danger to individuals if the possibility of lupus were ignored, later resulting in a damaging misdiagnosis. Tr. at 263. He also admitted that Petitioner's most recent lab work did not suggest she was still positive for the lupus anticoagulant, although Dr. Rose attributed that to her treatment with Rituximab. *Id*. at 268.

Given his conclusion that lupus was the proper diagnosis, Dr. Rose could not attribute the HPV vaccine to her condition, noting that valid epidemiological studies had found no association between lupus and HPV vaccination. First Rose Rep. at 6; Tr. at 201; *See generally* Chao; Thomas

Verstraeten, et al., *Analysis of Adverse Events of Potential Autoimmune Aetiology in a large Integrated Safety Database of AS04 Adjuvanted Vaccines*, 26 Vaccine 6630 (2008), filed as Ex. I (ECF No. 28-5) ("Verstraeten"). He reiterated the conclusions found in Chao, and added that in Verstraeten—a study of HPV among 68,512 people—there was no difference in the rates of autoimmune diseases among vaccinated people. First Rose Rep. at 6. However, as Petitioner pointed out in cross-examining Dr. Rose, Verstraeten relied on historical controls rather than an unvaccinated control group to make this comparison. Tr. at 243.

Dr. Rose also commented on the picture of Petitioner's skin after falling in the pool in May 2012 and hitting the side of the deck after her second HPV vaccine, which Petitioner had suggested was reflective of some initial reaction to the first HPV dose. He opined that the duration of the lesion had nothing to do with ITP. Tr. at 221. Moreover, he stated that thrombocytes exist to *prevent* bleeding, not to accelerate healing, thereby dismissing Petitioner's mother's contention that the long duration of the wound was evidence of ongoing ITP. *Id*.

2. Dr. Thomas G. Forsthuber

Respondent's second expert was Dr. Forsthuber, an immunologist, who testified at hearing and produced two expert reports in the case. *See* Forsthuber Expert Report, dated Nov. 18, 2015, filed as Ex. N (ECF No. 29-1)("First Forsthuber Rep."); Forsthuber Second Expert Report, dated Mar. 23, 2016, filed as Ex. KK (ECF No. 36-6)("Second Forsthuber Rep."); Tr. at 271-361.

Dr. Forsthuber received his medical degree from the University of Tübingen in Germany and then completed a post-doctoral fellowship in immunology at the University of California, Los Angeles. Tr. at 277; Forsthuber CV, filed as Exhibit O (ECF No. 29-2). He completed an additional post-doctoral fellowship at Case Western University in Cleveland, Ohio. Forsthuber CV at 2; Tr. at 278. He became a member of the faculty at the University of Texas, San Antonio, and began performing research in immunology and now runs a research lab that does T cell biology work and B cell immunology. *Id*. In addition, Dr. Forsthuber has published over 75 publications (reviews and book chapters) in the areas of T cell immunology and autoimmune diseases. First Forsthuber Rep. at 1.

Dr. Forsthuber's impression in this case was that the HPV vaccine doses that Petitioner received did not cause ITP or lupus. First Forsthuber Rep. at 10; Tr. at 276. His opinion was particularly focused on rebutting Dr. Shoenfeld's immunological conclusions. Dr. Forsthuber began by discussing the homology of the sequence (KATPTTS) suggested by Dr. Shoenfeld as common to both HPV antigens and the blood platelets, relying on Robert McMillan, *The Pathogenesis of Chronic Immune Thrombocytopenic Purpura*, 44 Seminars in Hematology (Supp. 5) S3 (2007), filed as Ex. W (ECF No. 30-1) ("McMillan"). The McMillan article reviewed the platelet autoantigens implicated in ITP. Tr. at 276. That article, however, did not state that the

receptor proposed by Dr. Shoenfeld (CB1q) is involved in the development of ITP. *Id*. at 277; First Forsthuber Rep. at 6.

In addition, Dr. Forsthuber opined that even if homology between an HPV vaccine component and structures on the platelet surface existed, the seven amino acid sequence proposed by Dr. Shoenfeld was "suboptimal" for the induction of T cell responses, which could induce an adverse event following vaccination. First Forsthuber Rep. at 6. He relied in part on Andre Silvanovich, et al., *The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity*, 90(1) Toxicological Sciences 252 (2006), filed as Ex. FFF (ECF No. 51-1), which found that among five, six, and seven amino acid sequences random matches with self protein sequences could readily be identified. The authors of that study concluded that in any amino acid sequences shorter than eight, finding a protein match was likely a chance occurrence or a random match, rather than reflecting true homology. Tr. at 287. It was also noted that the sequence proposed herein was not a unique one that only the HPV virus/vaccine expresses, but was somewhat common, occurring in other proteins. Tr. at 281. Specifically, Dr. Forsthuber pointed to the sequence's homology with EBV (a virus that Petitioner had at some time in her past), which is also implicated causally with ITP. *Id*. at 282.

Dr. Forsthuber attempted to further undermine Dr. Shoenfeld's theory of KATPTTS sequence homology allegedly found in C1qR and the HPV L1 protein by citing to a different article by Kanduc. *See* Darja Kanduc, et al., *Massive Peptide Sharing Between Viral and Human Proteomes*, 29 Peptides 1755 (2008), filed as Ex. MMM (ECF No. 59-5) ("Kanduc Two"). Unlike the Kanduc One article relied upon by Dr. Shoenfeld, Kanduc Two stated that homology (as suggested by Dr. Shoenfeld) was not a rare event—"importantly, the massive viral to human peptide overlapping calls into question the possibility of a direct casual association between virus-host sharing of amino acid sequences and incitement to autoimmune reactions through molecular recognition of motifs." Kanduc Two at 1755, 1765. This supported Dr. Forsthuber's overarching theory that there is little evidence to find that the HPV L1 protein is cross reactive with C1qR sufficient to cause ITP via molecular mimicry. Tr. at 313.

Dr. Forsthuber was also adamant that the timing in this case was not appropriate for vaccination causation. In his opinion, the onset of an autoimmune disease should occur within two to 28 days of the causal event. Tr. at 304. He therefore expected that once an antibody response is triggered by a vaccine, the drop in platelets would occur relatively quickly thereafter. *Id*. at 340. Dr. Forsthuber acknowledged, however, that in a condition like ITP the symptoms are often subclinical until the platelets drop low enough to produce obvious symptoms, like bruising or petechiae. *Id*. But he suspected that if Ms. Gramza's immune system had been creating antibodies against platelets in reaction to the HPV vaccine, that process should have occurred with her earlier vaccinations as well. *Id*. at 340-41.

IV. Procedural History

As noted above, this action was initiated in March 2015. Petition at 1. Thereafter, the case moved relatively quickly: a joint statement of completion was filed in April of that same year, and Respondent's Rule 4(c) Report was submitted in May. The parties next endeavored to find expert support for their respective positions, a process that was not complete until April 2016. I then scheduled the matter for hearing to be held from June 6-7, 2017. The parties made their pre-hearing filings, and the hearing was held as scheduled. I allowed the parties to file simultaneous post-hearing briefs, and this matter is now ripe for a decision.

V. Overview of Pertinent Medical Concepts

A. *ITP*

ITP is an autoimmune disease mediated by autoantibodies produced by B cells. Tr. at 83. Its clinical manifestation results from the destruction of platelets, which are pulled from the blood by the spleen or liver, resulting in a diminished number of platelets left to assist clotting. *Id*. at 85; Rinaldi at 2-3. ITP often is identified by the presence of petechiae, which are typically followed by bruising easily without an apparent cause or bleeding into organs. *Id*. The time course for ITP often varies depending on the age of the patient and the inciting agent. *Id*. at 86. The range for onset can vary from weeks to years. *Id*.

In adults, ITP (which tends to be chronic rather than the acute form children experience) can go unnoticed, as its primary symptom (a reduced platelet count) is often insidious, undiscovered except where a patient is under continuous surveillance by a physician, or if blood tests are performed and inadvertently reveal a low platelet count. Tr. at 86; G. Pamuk, et al., *Overview of 321 Patients with Idiopathic Thrombocytopenic Purpura: Retrospective Analysis of the Clinical Features and Response to Therapy*, 81 Annals of Hematology 436 (2002), filed as Ex. 17 (ECF No. 21-8).

Special masters in other Program cases alleging non-Table claims[17] have determined that it is possible for a vaccine to cause ITP, via the biologic mechanism of molecular mimicry. *Ebenstein v. Sec'y of Health & Human Servs.*, No. 06-573V, 2010 WL 5113185, at *21 (Fed. Cl. Spec. Mstr. Sept. 1, 2010) (accepting that molecular mimicry could plausibly link the MMR vaccine and ITP). I have similarly found that a petitioner presented sufficient evidence to conclude that it was possible for the HPV vaccine to cause ITP. *Johnson v. Sec'y of Health & Human Servs.*, No. 14-113V, 2017 WL 772534 (Fed. Cl. Spec. Mstr. Jan. 6, 2017).

[17] The Vaccine Injury Table also includes claims for ITP beginning 7-30 days after receipt of a vaccine containing the measles or rubella viruses.

B. *Lupus*

Lupus is an autoimmune condition featuring more identified autoantibodies than nearly all other autoimmune diseases. Tr. at 180; John Harley & Judith James, *Epstein-Barr Virus Infection Induces Lupus Autoimmunity*, 64 Bulletin of the NYU Hospital for Joint Diseases 45 (2006), filed as Ex. L (ECF No. 28-8). Its clinical appearance can be on a spectrum of severity. Some patients suffer from symptoms for a sustained period of time, only experiencing mild rashes, arthritis, and positive antibodies. Tr. at 180. Others, by contrast, may have symptoms revealing central nervous system damage, and can present with stroke or coma. *Id*. at 181. There may also be patients who have lupus but the effects are limited to the blood, which never amounts to full-blown lupus. *Id*.

Most physicians believe that lupus is idiopathic because there has not been proven to be one specific mechanism or etiology for the disease. Tr. at 182. Often however, there is a genetic component that either predisposes the patient to lupus, or a demonstrated family history of lupus (or other similar diseases). *Id*. The studies performed in the Chao and Verstraeten articles did not find an increased risk for autoimmune disorders— of which lupus is one—associated with adjuvanted vaccines like the HPV vaccine. Chao at 199; Verstraeten at 6637.

VI. Applicable Legal Standards

A. *Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury" – i.e., an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006).[18] In this case, Petitioner does not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(a)(1)(A). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*,

[18] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs*., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim (which is the kind of claim asserted in this matter), a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, the petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id*. at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*,

569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd,* 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id*. at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Law Governing Factual Determinations*

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as "the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such a determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Human Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs*., No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs*., 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms. It is equally unlikely that pediatric neurologists, who are trained in taking medical histories concerning the onset of neurologically significant symptoms, would consistently but erroneously report the onset of seizures a week after they in fact occurred").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs*., No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneously medical records are generally found to be deserving of greater evidentiary weight than oral testimony – especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F.2d

1226 (Fed. Cir.), *cert. den'd, Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y Health & Human Servs*., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records over contrary testimony, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc*., 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or

technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742-45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339).

D. *Consideration of Medical Literature*

Both parties relied on numerous pieces of medical and scientific literature in this case to support their respective positions. I have reviewed all of the medical literature submitted in this case, although my decision does not discuss each filed article in detail. *Moriarty v. Sec'y of Health & Human Servs.*, No. 2015-5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted).

ANALYSIS

In this matter, Petitioner has successfully established some disputed factual matters, as well as certain *Althen* prongs. But she has not carried her overall burden of proof to establish it "more likely than not" that the HPV vaccine caused her ITP. I address the factors relevant to my determination in order of their significance to the holding, rather than in the order presented by *Althen*.

I. *Althen* Prong Three

Resolution of this case largely turns on the timing of onset of Ms. Gramza's ITP after her receipt of the HPV vaccines, and determining if that onset is medically acceptable (assuming for the moment that the HPV vaccine "can cause" ITP). The Vaccine Act's statute of limitations (which in an indirect way defines what constitutes onset) for claims like the present runs from "the date of the occurrence of the first symptom or manifestation of onset . . . ." Section 16(a)(2). As noted by the Federal Circuit, determining onset "does not depend on when a petitioner knew or reasonably should have known anything adverse about her condition." *Cloer v. Sec'y of Health & Human Servs.*, 654 F.3d 1322, 1339 (Fed.Cir.2011) (*en banc*). Thus, the medical *discovery* that an injured party has a particular illness or condition does not define onset – the first presenting symptoms or manifestations do.

Determining the onset for a condition like chronic ITP is a difficult task. A drop in platelet count is invisible to the eye, and an individual suffering with ITP could live with the drop for some time before either experiencing a physical manifestation (i.e. bruising) or inadvertently learning of it after a blood test. However, it has been noted in other decisions that this fact cuts both ways, making it difficult to negate the possibility, even in cases in which a physical manifestation of ITP is seen post-vaccination, that the process could have begun *before* the vaccine at issue was administered. *Doyle v. Sec'y of Health & Human Servs.*, 92 Fed. Cl. 1, 4 and 7 (onset of ITP six months after the MMR vaccine was too attenuated for causation); *see also Johnson*, 2017 WL 772534, at *17-18 (discussing *Doyle* and finding that petitioner's expert could not reliably establish that onset of ITP occurred post-vaccination simply on the basis of post-vaccination discovery of platelet drop). Because of this, evidence of an initial physical manifestation of ITP is likely the most reliable proof of onset available.

Here, there is some discrepancy between the medical records and witness testimony on the onset question. Although no platelet count testing was performed prior to Petitioner's February 2014 doctor's visit (which occurred over a year after the last dose of Gardasil), statements from Petitioner and Petitioner's mother to treaters at that time – when Ms. Gramza first sought medical intervention for the symptoms later determined to be ITP - place onset in July 2013, based on assertions that her symptoms (heavy periods, bruising, etc.) had persisted for the prior six months. *See, e.g.*, Ex. 3 at 15, 59-61; Ex. 4 at 86. If so, then onset began six months after vaccination, with

another six or seven months passing before medical intervention was sought (a reasonable lapse, given the insidious and mild nature of chronic ITP akin to what Petitioner seems to have been experiencing).

Ms. Gramza and her mother gave testimony that was inconsistent on this point. On the one hand, both fact witnesses vividly recalled the July 2013 Hawaii trip incident, which matches the medical records suggesting onset as having begun around that time. Ms. Gramza's testimony, however, moved onset slightly earlier, to March 2013, when she claimed she began noticing that she was bruising easily. Tr. at 60. Mrs. Gramza also confirmed this earlier onset time. Tr. at 12-13.[19] But a March 2013 onset (which would be considerably closer in time to the last HPV vaccination) is not corroborated by any medical records. Moreover, while I can accept that Petitioner and her mother may have delayed treatment due to a misapprehension as to the seriousness of the condition, the length of time they waited for treatment is increased to nearly *nine months* if I accept their allegations of a March 2013 onset – a far longer, less credible delay, especially if the purported March symptoms were followed by the July 2013 incident, and then continued for the remainder of the year.

Taking all of the above into account, I find the evidence best supports the conclusion that the outward symptoms of Ms. Gramza's ITP were observed no earlier than July 2013, making it the effective onset date for purposes of this claim. That date has the most ample support in the medical records and the witness testimony.

I now turn to whether that onset – occurring approximately six months after her last HPV dose – is a medically acceptable timeframe in which the alleged autoimmune process could have occurred. Dr. Shoenfeld opined that an autoimmune reaction of this type could take many weeks, months, or even years to develop. Tr. 139-41. To support this contention he relied on literature that reported long onset between vaccine and injury, but not involving injuries relevant to this case. *See, e.g.,* C. Poser & P. Behan, *Late Onset of Guillain Barré Syndrome,* 3 J Neuroimmunology 27 (1982), filed as Ex. 42 (ECF No. 24-3)(showing cases of Guillain-Barré syndrome that occurred week to months after a precipitating cause); R. Gherardi & F. Authier, *Macrophagic Myofasciitis: Characterization and Pathophysiology,* 21 Lupus 184 (2012), filed as Ex. 43 (ECF No. 24-4) (a study finding the onset of symptoms of macrophagic myofasciitis (a condition characterized by chronic fatigue, myalgia, and cognitive dysfunction) began at seven months post-vaccination) ; R. Gherardi & F. Authier, *Aluminum Inclusion Macrophagic Myofasciitis: A Recently Identified*

[19] I do not find persuasive, however, Petitioner's suggestion that she experienced an ITP symptom in connection with her swimming pool accident in the summer of 2012. The photo offered into evidence does not support the contention that the hematoma she experienced was more likely than not due to ITP rather than the fall itself.

Condition, 23 Immunology Allergy Clinics of North America 699 (2003), filed as Ex. 44 (ECF No. 24-5).[20]

Dr. Forsthuber, by contrast, allowed for a timeframe of up to 28 days after vaccination for onset of an autoimmune condition like ITP. Tr. at 303-04. Although Dr. Forsthuber did not rule out the possibility of an even longer interval occurring in some cases, he opined that the further past four weeks, the more unlikely that the vaccine could be deemed causal. *Id*. at 304. Other Program decisions (including a case I decided) have allowed for onset of ITP up to six weeks post-vaccination. *See, e.g., Johnson,* 2017 WL 772534, at *16 (an autoimmune process such as ITP would most likely occur within 42 days after vaccination), *citing Ebenstein*, 2010 WL 5113185, at *21 (five and one-half to six weeks is "plausible" for ITP to occur after the MMR vaccine); *Doyle v. Sec'y of Health & Human Servs.*, No. 05-605V, 2009 WL 2973106 (onset of ITP six months after the MMR vaccine was too attenuated for causation); *mot. for review den'd,* 92 Fed. Cl. 1 (2010).

Based on the expert testimony plus the well-reasoned decisions cited above involving ITP, I find that Petitioner has not demonstrated that the July 2013 onset for her ITP occurred in a medically-acceptable timeframe six months after receipt of the third HPV dose in January 2013. A timeframe of four to six weeks post-vaccination has far more support, and Petitioner's expert did not persuasively establish otherwise. Accordingly, she has not offered sufficient evidence for me to find it more likely than not that this *Althen* prong is satisfied.[21]

II. *Althen* Prong Two

As a threshold issue, I find that the record better supports the conclusion that Petitioner's illness was ITP rather than lupus. Although treaters reasonably included lupus in their initial

[20] Dr. Shoenfeld has also in other cases put forward the particularly unpersuasive contention that virtually *any* timeframe post-vaccination is medically acceptable for onset of an autoimmune condition. *See, e.g., Garner v. Sec'y of Health &Human Servs.,* No. 15-063, 2017 WL 1713184, at *16-17 (Fed. Cl. Spec. Mstr. Mar. 24, 2017); *Hennessey v. Sec'y of Health & Human Servs.*, 91 Fed.Cl. 126, 142 (2010) (rejecting Dr. Shoenfeld's attempt to satisfy the third prong by positing that any timeframe is appropriate).

[21] Petitioner might argue in response that, due to ITP's insidious character, the fact that Ms. Gramza first experienced excessive bleeding in July 2013 does not mean that the autoimmune process causing the platelet destruction she experienced did not begin *sooner* – and hence closer in time to the vaccination, thereby increasing the causal potential of the HPV vaccine. Such an argument, however, runs head-on into an equally-reasonable counter-explanation (allowed for by Dr. Shoenfeld's expansive view of autoimmune disease onset): that her ITP might have begun *before* vaccination. Petitioner maintains that it took six months before she experienced an outward symptom, but that her overall course was mild enough that she delayed treatment for another six months. But it could equally be concluded that the autoimmune process that resulted in the July 2013 incident had been subclinical many months *before* the first instance of bleeding, which means before the last dose of HPV vaccine received in January 2013. All of the above underscores why in such a case determining the first manifestation of a symptom associated with ITP is the most legally-reliable method of determining onset.

differential diagnoses, based on certain test results and on a sound medical understanding about ITP's relationship to lupus, the medical record ultimately does not confirm the diagnosis. Dr. Rose was not persuasive in establishing that Ms. Gramza's symptoms met the lupus clinical criteria, while Dr. Shoenfeld (despite his initial embrace of that diagnosis) did credibly explain how the record did not corroborate Dr. Rose's opinion, based on Petitioner's overall history since the time her ITP was first confirmed by blood testing in 2014.

But even though I accept Petitioner's argument as to the nature of her condition, I do not find that she has successfully established that the HPV vaccine "did cause" her ITP. Other than observing that her symptoms presented temporally after receipt of the HPV vaccine, Petitioner has not provided a compelling narrative, built from facts set forth in the medical record, establishing a "logical sequence of cause and effect" associating vaccine to injury. No treaters ever proposed a relationship between the HPV vaccine and Petitioner's ITP, and beyond her symptoms Petitioner points to nothing in her medical records that would corroborate the allegation that beginning in the summer of 2013 she was experiencing a vaccine-induced autoimmune process. And there is also some admittedly-inconclusive evidence suggestive of alternative causes for her condition (for example, her EBV titers measured around the time her platelet count was first performed, or the "red flag" blood testing results obtained by Dr. Shah that supported a lupus diagnosis), which was ineffectively rebutted by Petitioner, further diminishing the strength of Petitioner's evidentiary showing (even if this evidence does not itself stand as preponderant proof of an alternative cause).

The analytic concept of challenge/re-challenge helps to underscore the deficiencies of Petitioner's "did cause" *Althen* showing. Evidence that Ms. Gramza's immunologic reaction to the HPV vaccine increased in strength and rapidity with each dose would corroborate the argument that the vaccine was acting upon her as theorized. Yet the medical record in this case does not reflect this occurring. At best, four months passed from Petitioner's first receipt of HPV vaccine to the pool injury that she alleges was evidence of an initial reaction – yet there was no reaction at all reflected in the records between the second dose (received July 2012) and third (received January 2013), and the earliest reaction after the last dose was in the spring of 2013 (although I have found the record better supports an even later onset, in July 2013). Were challenge/re-challenge occurring, each reaction should have been *closer* in time to the next dose. I therefore do not conclude that preponderant evidence supports the determination that the HPV vaccine was the "but for" cause of Petitioner's ITP.

III. *Althen* Prong One

The "can cause" prong is the only component of Petitioner's case that I find she successfully established. Admittedly, Respondent offered some persuasive, robust items of epidemiologic evidence suggesting that the HPV vaccine is not associated with autoimmune conditions like ITP. Dr. Forsthuber also raised reasonable questions about the plausibility of components of the HPV vaccine cross-reacting as alleged herein. At the same time, it is fairly well

established in other Program decisions that ITP (understood to be an autoimmune condition) has been credibly associated with vaccination, and the HPV vaccine as well – and the decisions of other special masters (including my own) have embraced as reliable the science supporting such contentions. Weighing all of the above, I find that Petitioner, through the testimony of her expert, Dr. Shoenfeld, did persuasively establish in this case that the HPV vaccine could cause ITP. But because the other two *Althen* prongs (and in particular the third) were not met, success in meeting this component of Petitioner's case was by itself not enough to meet her overall burden of proof.

CONCLUSION

The record does not support Petitioner's contention that the HPV vaccines she received caused her ITP, and/or did so in a medically acceptable timeframe. Petitioner has not established entitlement to a damages award, and therefore I must **DISMISS** her claim.

In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accordance with this decision.[22]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Special Master

[22] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by filing a joint notice renouncing their right to seek review.